Prophylactic function of excellent compliance with LTOT in the development of pulmonary hypertension due to COPD with hypoxemia

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Abstract

The long-term oxygen therapy (LTOT) for patients with chronic obstructive pulmonary disease (COPD) has been shown to increase survival in patients with severe resting hypoxemia. The adherence to LTOT may also simultaneously affect the development of concomitant pulmonary hypertension (PH) due to COPD with hypoxemia. We retrospectively reviewed 276 cases of COPD with or without PH assessed by right heart catheterization (RHC) to investigate whether adherence to continuous LTOT had a prophylactic effect on the development of PH in a time interval of two years. In contrast to the patients in the non-compliance group (PH prevalence 64.2%), patients with excellent compliance of adhering to continuous LTOT > 15 h per day in the compliance group (PH prevalence 37.6%) are more liable to postpone the development of PH due to hypoxic COPD for at least two years. Adherence to LTOT $\geq$ 15 h/day is strongly recommended in order to lower the risk and delay the development of consequent PH in COPD with hypoxemia.

Introduction

Chronic obstructive pulmonary disease (COPD) has become the third leading cause of death worldwide and is estimated to become the disease with the seventh greatest burden worldwide in 2030. Many people suffer from this disease for years and die prematurely from it or its complications,[1–3] in which pulmonary hypertension (PH) may develop late in the course of COPD and is due mainly to hypoxic vasoconstriction of the small pulmonary arteries, eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy.[4–6] PH is a pathophysiological disorder that may involve multiple clinical conditions and can complicate the majority of cardiovascular and respiratory diseases.[7] The most common lung diseases associated with PH are COPD, interstitial lung disease (ILD), and combined pulmonary fibrosis and emphysema (CPFE).[8–10] Mild PH is common in both severe ILD and severe COPD.[11] In COPD, the development of PH is accompanied by a deterioration of exercise capacity, worsening of hypoxemia, and shorter survival.[6,8–10]

Therefore, the prophylaxis of development of PH due to COPD beforehand is definitely crucial and better than the remedy afterwards for this patient population. It has been well recognized that long-term oxygen therapy (LTOT) administration can partially reduce, attenuate, and sometimes reverse the progression of PH in COPD. The longer the daily duration of LTOT, the better the hemodynamic results, notwithstanding PAP rarely returns to normal values and the structural abnormalities of pulmonary vessels

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remain unaltered or patients' compliance issues.[12–14] Therefore, besides the alleviating function of LTOT in the developed PH due to hypoxic COPD, we speculated that LTOT might possess prophylactic function in the process of development of PH due to hypoxic COPD since the progression of COPD-related PH may be ameliorated by LTOT. Nevertheless, to the best of our knowledge, no existing studies have examined this subject to date. It was the purpose of this study to answer the question.

Methods

Study design

We designed a retrospective analysis to review a consecutive cohort of COPD patients with or without PH assessed by right heart catheterization (RHC) to explore the potential intervening effect of LTOT in the prevention and suspension of development of PH in the past two years before enrollment in October 2017. All requisite data comprising information in the case notes and test results were retrieved from the database of the Department of Cardiopulmonary Circulation of Shanghai Pulmonary Hospital Tongji University which is one of the major PH centers in China. All relevant medical history in the case notes were documented by the patients' attending physicians who had abundant clinical experience in the management of COPD and PH. All performed tests were conducted by professional personnel under standard operating procedure. This protocol was approved by the institutional review board of Shanghai Pulmonary Hospital.

Study population

This cohort of patients was registered in a registry for COPD patients who underwent RHC in the Department of Cardiopulmonary Circulation of Shanghai Pulmonary Hospital between May 2015 and October 2017 due to at least one of the following reasons: (1) episodes of right ventricular failure or suspected PH by echocardiographic findings; (2) suspected pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH); (3) candidates for lung transplantation or lung volume reduction. This cohort of COPD patients were regularly self-managed as usual and followed up at least trimonthly at our clinics for routine checkup and hospitalized while necessary in this hospital for a long term (at least three years). The data were collected at each follow-up. All eligible patients being studied were screened out by the inclusion and exclusion criteria.

Inclusion criteria consisted of the following requirements for eligible patients: (1) before baseline, which was defined as two years before enrollment, the patient had a diagnosis of COPD, defined as an FEV_1:FVC ratio of <0.70 after bronchodilator use plus respiratory symptoms, a history of exposure to risk factors (e.g. smoking, air pollution, biomass combustion), or both, measured 20 min after the inhalation of 400 ug of albuterol (Ventolin,Glaxo Wellcome);[15] (2) a medical history of absence of PH, defined as mean pulmonary arterial pressure (mPAP) < 25 mmHg at rest assessed by RHC at baseline;[7] (3) an indication of LTOT defined as PaO_2 < 55 mmHg or SaO_2 < 88% or PaO_2 > 55 but < 60 mmHg with erythrocytosis (erythrocyte > 6.0×10^{12}/L for men; erythrocyte > 5.5×10^{12}/L for women) at baseline along with a prescription of continuous LTOT by nasal cannula for 24 h or at least 15 h per day at 2 L/min or adjusted higher to maintain an SpO_2 of 90% or more if necessary with stationary and/or portable oxygen concentrators from baseline to enrollment.[15,16] In case patients had an indication for LTOT, the oxygen would be given to them for the sake of safety in the process of RHC. All patients received regular long-term inhalation therapies with proper inhalation technique from prescribers when regimens were given, according to the COPD groups they were in, by the individualized assessment of symptoms and exacerbation risk, from baseline to enrollment; (4) a diagnosis with or without PH at enrollment, defined as a mPAP ≥25 mmHg, as well as a pulmonary artery wedge pressure (PAWP) ≤15 mmHg or mPAP <25 mmHg at rest as assessed by RHC;[7] along with the assessment of World Health Organization functional class (WHO FC), 6-min walking distance (6MWD), peak VO_2 in cardiopulmonary exercise testing (CPET), as well as N-terminal pro-brain natriuretic peptide (NT-proBNP) for all patients at enrollment. The evidence of negative PH and indication of LTOT at baseline were collected within six months before baseline.

Exclusion criteria consisted of the following requirements from baseline to enrollment: (1) a diagnosis of other chronic lung diseases such as asthma, asthma-COPD overlap (ACO), ILD, CPFE, bronchiectasis, tuberculosis, obliterative bronchiolitis, diffuse panbronchiolitis, some connective tissue diseases such as Langerhans cell granulomatosis, sarcoidosis, and/or other severe systemic diseases such as congestive heart failure;[7,15] (2) a diagnosis of PH in Group 1, Group 2, Group 4, and Group 5 according to classifications in 2015 ESC/ERS PH guidelines;[7] (3) having ever received continuous LTOT more than six months before baseline; and (4) absence of any data involved in the review analysis.

Assessment

The primary assessment was the comparison of demographics, COPD-related variables at baseline, and PH prevalence, parameters in RHC, WHO FC, 6MWD, peak VO_2 in CPET, NT-proBNP, as well as exacerbations counting per year at enrollment between the compliance and noncompliance groups. The compliance group was defined as a group of patients whose self-reported average daily use of LTOT ≥15 h/day by means of recording serial meter readings on oxygen concentrators every day, whereas the noncompliance group was defined as LTOT <15 h/day. The detailed information of the LTOT status were provided by

the patients or their family members by means of recording the readings on oxygenators at each follow-up. Then the average usage of LTOT were calculated for the last three months. Exacerbation was defined as an acute worsening of respiratory symptoms that result in additional therapy.[17,18] The self-reported compliance status and exacerbation frequency of patients in the past two years before the study were documented in patients' case notes at the previous follow-ups, hospitalizations, and enrollment by patients' attending physicians. The secondary assessment was the comparison of demographics, COPD-related variables at baseline, average daily use of LTOT, mPAP, as well as exacerbation count per year between the PH-positive and PH-negative group. The last assessment was the correlation analysis between demographics, COPD-related variables, as well as compliance and the development of PH.

Statistical analysis

Measurement data were presented as mean ± standard deviation or median with interquartile range where appropriate. Categorical data were presented as frequencies and percentages. The comparison of continuous variables between two groups was conducted with a t-test. The comparison of the rate between two groups was conducted with a Chi-square test. We conducted a univariate and a multivariate Cox regression analyses to calculate odds ratio (OR) and 95% confidence intervals (CI) for each predictive parameter as a variable. Statistical significance was accepted at $P < 0.05$.

Results

Demographics and characteristics of the patients

After the exclusion of 25 cases with a diagnosis of other chronic lung diseases, 20 cases with a diagnosis of PH in Group 1, Group 2, Group 4, or Group 5, and 18 cases missing data involved in the review analysis, among 339 cases of hypoxic COPD with or without PH assessed by RHC, a total of 276 patients were eligible for the final full analysis set. The overall mean age and female:male ratio of all eligible patients were 67.6 years and 90:186, respectively. At baseline, there were 170 (61.6%) in the compliance group and 106 (38.4%) in the non-compliance group. Almost all cases received RHC before LTOT; only a few cases (n = 10) received less than three months of LTOT before RHC. The mean usage period was 2.2 months. No statistical difference was found between the compliance and non-compliance groups in regard to age, sex ratio, body mass index (BMI), FEV_1, GOLD stages, COPD groups, and mPAP at baseline ($P > 0.05$ for all comparisons), except CAT score in the compliance group was higher than that in the non-compliance group ($P = 0.005$). The average daily use of LTOT in the compliance group and

non-compliance group were 19.6 and 12.8 h, respectively ($P = 0.003$). Basically, the patients adopted LTOT every day due to their condition. In case of irregular adherence, education would be provided in order to persuade patients to comply with prescriptions. However, it produced little effect. During the two-year interval, the average exacerbation count per year was 1.4 and 2.5 in the compliance and non-compliance groups, respectively ($P = 0.032$). At enrollment, 144 (52.2%) were diagnosed without PH, whereas 132 (47.8%) were diagnosed with PH, in which 64 cases (prevalence 37.6%) were in the compliance group and 68 cases (prevalence 64.2%) were in the non-compliance group ($P < 0.001$). The mPAP of the compliance group versus the non-compliance group increased from 16.6 mmHg versus 18.3 mmHg ($P = 0.538$) to 20.6 mmHg versus 28.9 mmHg ($P = 0.005$), respectively. The mPAP alteration was 4.0 mmHg and 10.6 mmHg in the compliance and non-compliance groups, respectively ($P < 0.001$). The PH-positive group had a higher proportion of women, GOLD 4, group D, exacerbation counts, as well as mPAP as expected, and lower FEV_1 of the predicted value, average daily use of LTOT, as well as the proportion of patients with compliance by contrast with PH-negative group. The demographics and characteristics of the patients are summarized in Table 1.

Comparison between different compliance groups

The comparison between different compliance groups in regard to PH-related variables at enrollment demonstrated that the proportion of WHO FC I or II in the compliance group was higher than that in the non-compliance group, whereas the proportion of WHO FC III or IV in the non-compliance group was higher than those in the compliance group ($P < 0.05$ for all). For other variables, mPAP, RAP, and NT-proBNP in the compliance group were lower than those in the non-compliance group, whereas SVO_2 and peak VO_2 in the compliance group were higher than those in the non-compliance group, except no statistical difference was found regarding CI and 6MWD (Table 2). In a subgroup comparison between compliance (64 cases) and non-compliance (68 cases) subgroups in all PH-positive patients, no statistical difference was found with respect to the average daily use of LTOT, WHO FC, mPAP, RAP, CI, SVO_2, 6MWD, peak VO_2, and NT-proBNP ($P > 0.05$ for all comparisons) (Table 3).

Correlation between variables and the development of PH

A univariate analysis demonstrated that sex ratio, FEV_1, non-compliance with LTOT, GOLD stage, and COPD groups as well as exacerbations were all correlated with the development of PH due to hypoxic COPD. After adjusting for the influence of age, sex, BMI, and smoking status, in a multivariate analysis, the significance between FEV_1 and

Table 1. Demographics and characteristics of the patients.

Variables	Compliance (n = 170)	Non-compliance (n = 106)	P value	PH-positive (n = 132)	PH-negative (n = 144)	P value
Age (years)	68.3 ± 10.5	66.9 ± 11.3	0.373	68.9 ± 11.2	66.3 ± 11.8	0.618
Women/Men (n)	56/114	34/72	0.088	50/82	40/104	0.001
Smoker/Non-smoker (n)	142/28	90/16	>0.05 for all	112/20	120/24	0.161
BMI (kg/m^2)	22.8 ± 6.5	23.3 ± 5.8	0.638	22.2 ± 6.6	23.9 ± 6.3	0.532
FEV$_1$ (% of predicted value)	35.8 ± 28.3	33.9 ± 26.4	0.532	30.5 ± 26.8	39.2 ± 27.2	0.044
GOLD (1/2/3/4) (%)	0/5.9/50.6/43.5	0/5.7/50.9/43.4	>0.05 for all	0/4.5/37.9/57.6	0/6.9/62.5/30.6	<0.05 for GOLD 3,4
Group (A/B/C/D) (%)	0/28.2/32.9/38.9	0/30.2/34.0/35.8	>0.05 for all	0/9.1/24.2/66.7	0/47.2/41.7/11.1	<0.05 for all
CAT score (points)	24.8 ± 15.3	16.6 ± 14.1	0.005	21.2 ± 16.8	20.2 ± 15.4	0.061
Daily use of LTOT (h)	19.6 ± 4.3	12.8 ± 4.7	0.003	12.5 ± 5.1	19.9 ± 4.9	0.002
mPAP at baseline (mmHg)	16.6 ± 5.4	18.3 ± 6.6	0.538	18.1 ± 5.8	16.8 ± 6.3	0.095
mPAP at enrollment (mmHg)	20.6 ± 6.8	28.9 ± 7.3	0.005	31.0 ± 5.2	18.5 ± 6.3	<0.001
mPAP change	4.0 ± 2.6	10.6 ± 3.6	<0.001	12.9 ± 5.7	1.7 ± 1.5	<0.001
PAWP (mmHg)	9.1 ± 5.4	10.8 ± 6.2	0.638	9.5 ± 6.6	10.4 ± 5.8	0.545
Exacerbations	1.4 ± 1.2	2.5 ± 1.3	0.032	2.6 ± 1.3	1.3 ± 1.4	0.019
PH+/PH− (%)	37.6/62.4	64.2/35.8	<0.001 for both			
Compliance/Non-compliance (%)				48.5/51.5	73.6/26.4	<0.001 for both

PH, pulmonary hypertension; BMI, body mass index; FEV$_1$, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, COPD assessment test; LTOT, long-term oxygen therapy; mPAP, mean pulmonary arterial pressure.

Table 2. Comparison of PH-related variables between different compliance groups at enrollment.

Variables	Compliance (n = 170)	Non-compliance (n = 106)	P value
WHO FC (I/II/III/IV) (%)	25.9/38.8/27.1/8.2	15.1/24.5/35.8/24.6	<0.05 for all
RAP (mmHg)	5.9 ± 3.6	11.3 ± 4.5	<0.001
CI (L/min/m^2)	2.7 ± 1.8	2.4 ± 1.6	0.099
SVO$_2$ (%)	69.8 ± 6.8	59.6 ± 6.8	0.036
6MWD (m)	386.5 ± 66.8	367.3 ± 59.6	0.081
Peak VO$_2$ (mL/min/kg)	16.8 ± 6.3	11.6 ± 6.9	0.025
NT-proBNP (ng/L)	313.1 ± 128.7	816.5 ± 147.3	<0.001
FEV$_1$ of predicted (%)	36.9 ± 16.5	34.6 ± 18.1	0.532
PaO$_2$ (mmHg)	58.3 ± 25.2	42.4 ± 27.6	0.005

WHO FC, World Health Organization functional class; RAP, right atrial pressure; CI, cardiac index; SVO$_2$, mixed venous oxygen saturation; 6MWD, 6-min walking distance; peak VO$_2$, peak oxygen consumption; NT-proBNP, N-terminal pro-brain natriuretic peptide.

non-compliance with LTOT (1.816 [1.298–2.357], $P = 0.002$) GOLD stage, and COPD groups as well as exacerbations and the development of PH due to hypoxic COPD still remained (Table 4).

Discussion

Being different from inhalation therapies, LTOT is tedious, shackling, frustrating, and money-consuming for patients resulting in poor compliance. In this study, we investigated the prophylactic effect of excellent compliance with LTOT in preventing the development of PH due to COPD with hypoxemia. In view of no comparable studies being available, all we have is this study to discuss. The results of this study demonstrated that adherence to continuous LTOT ≥15 h per day could preferably suspend the development of PH due to COPD for at least two years compared with the non-compliance group in which the patients had LTOT <15 h per day.

To start with the demographics, in the comparison between different compliance groups at baseline, the results demonstrated that the homogeneity of patients was quite considerable in regard to age, sex, smoking status, BMI, GOLD stage, COPD group, and mPAP of the patients

Table 3. Comparison of PH-related variables between different compliance groups in PH-positive patients at enrollment.

Variables	Compliance (n = 64)	Non-compliance (n = 68)	P value
Daily use of LTOT (h)	15.7 ± 3.2	12.3 ± 3.5	0.088
WHO FC (I/II/III/IV) (%)	18.8/31.3/34.3/15.6	17.6/29.4/35.3/17.5	>0.05 for all
mPAP (mmHg)	29.5 ± 5.3	31.3 ± 5.6	0.098
RAP (mmHg)	11.9 ± 3.9	11.3 ± 4.5	0.164
CI (L/min/m^2)	2.2 ± 1.5	2.1 ± 1.4	0.106
SVO$_2$ (%)	63.6 ± 7.0	61.4 ± 6.4	0.062
6MWD (m)	339.7 ± 72.5	308.8 ± 68.3	0.071
Peak VO$_2$ (mL/min/kg)	13.8 ± 6.7	13.6 ± 6.1	0.152
NT-proBNP (ng/L)	843.4 ± 226.5	884.8 ± 213.6	0.076

PH, pulmonary hypertension; LTOT, long-term oxygen therapy; WHO FC, World Health Organization functional class; mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; CI, cardiac index; SVO$_2$, mixed venous oxygen saturation; 6MWD, 6-min walking distance; peak VO$_2$, peak oxygen consumption; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 4. Correlation between variables and the development of PH in COPD with hypoxemia.

Variable	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per increase of 10 years)	1.116 (0.817–1.421)	0.096		
Male	1 (reference)			
Female	1.558 (1.032–1.976)	0.022		
Non-smoker	1 (reference)			
Smoker	1.120 (0.737–1.321)	0.078		
BMI (per decrease of 1 kg/m^2)	1.089 (0.897–1.324)	0.438		
FEV$_1$ (per decrease of 10% of predicted value)	1.642 (1.110–1.956)	0.018	1.658 (1.146–1.978)	0.005
Compliance to LTOT	1 (reference)			
Non-compliance to LTOT	1.707 (1.276–2.218)	0.004	1.816 (1.298–2.357)	0.002
GOLD (per progression of 1 stage)	4.960 (3.787–5.161)	<0.001	4.731 (3.521–5.007)	<0.001
Groups (per progression of 1 group)	2.708 (2.356–3.751)	<0.001	2.636 (2.227–3.646)	<0.001
Exacerbations (per increase of 1 AE)	2.010 (1.534–2.617)	0.002	1.904 (1.433–2.523)	0.002
CAT score (per increase of 5 points)	1.050 (0.916–1.248)	0.516		

PH, pulmonary hypertension; BMI, body mass index; FEV$_1$, forced expiratory volume in 1 s; LTOT, long-term oxygen therapy; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, COPD assessment test.

except for CAT score. The comparison then showed that the compliance group achieved longer average daily use of LTOT and consequent lower exacerbation frequency, PH prevalence, mPAP at enrollment, as well as mPAP increase compared with the non-compliance group. For the comparison between PH-positive and PH-negative groups, the results demonstrated that the PH-positive group had more female patients, advanced GOLD stage, senior group, exacerbation count, as well as expected mPAP, and less FEV$_1$ of the predicted value, average daily use of LTOT, as well as compliance by contrast with PH-negative group. This result indicated that hypoxic COPD-related PH which can be regarded as a co-morbidity of COPD was literally due to COPD progressing to the advanced stage. The more severe the stage, the higher the probability of developing PH, otherwise another

underlying cause must be sought especially under the circumstances of concomitant mild COPD with severe PH.[7] Since hypoxic vasoconstriction of small pulmonary arteries is the major cause in the pathophysiological mechanism of PH due to hypoxic COPD,[4] logically, it does make sense that adherence to continuous LTOT is efficacious in the prophylaxis of development of PH due to COPD with hypoxemia.

We noted that the change in mPAP was relatively high and reckoned that this was partially due to the majority of our patients belonging to GOLD 3 and 4 and group C and D in which patients had advanced COPD, and also due to the limited sample size. The parameters regarding the respect of COPD, such as FEV$_1$ were similar among the four groups, suggesting the progression of the COPD itself was similar among the four groups. In other words, COPD

per se impacts mPAP of all four groups in a like manner. As for PaO2, the compliance group was higher than the non-compliance group. We reckon that LTOT may impact hypoxemia or parameters relevant to oxygen therapy more than airflow limitation.

It is worth mentioning that the CAT score, which was higher in the compliance group than in the non-compliance group, was simultaneously similar between the PH-positive and PH-negative groups. After the discussion, we realized that the CAT score did not only reflect the severity of disease, but also influenced patients' treatment-seeking incentives which determined how their compliance was, consequently compromising its prompt effect in the development of PH. The compliance of patients is up to their subjective perception instead of the actual severity. Somatic discomfort such as breathlessness due to hypoxemia impels patients' adherence to the regimens such as LTOT which can immediately alleviate their symptoms. Dyspnea can be regarded as a protective response towards hypoxemia. Lack of vigilance due to inconspicuous symptomatic signaling is the chief culprit for poor compliance, regrettably leading to poorer outcome and prognosis which could have been avoidable and preventable. Therefore, for COPD patients without severe subjective perception in the advanced stage, the supervision and monitoring should be strengthened even more than for patients with severe subjective perception in their condition management.

The next comparison of PH-related variables between different compliance groups at enrollment showed that, except for 6MWD and CI, all other PH-related variables in the compliance group were better than those in the non-compliance group, being consistent with their different PH prevalences. Excellent compliance with continuous LTOT was beneficial to maintain mPAP, improve functional class, hemodynamics as well as exercise capacity parameters along with the decrease of PH prevalence in hypoxic COPD compared with poor compliance. For the negative response of 6MWD and CI, we speculated that 6MWD is a sub-maximal exercise test influenced by several factors, including sex, age, height, weight, co-morbidities, need for O_2, learning curve, and motivation;[7] meanwhile, CI has too small cardinal number to be differentiated between the two groups. For the next subgroup comparison between different compliance groups in PH-positive patients, the results showed that no statistical difference was found either regarding average daily use of LTOT or regarding PH-related variables, suggesting those PH-positive patients in the compliance group were patients with compliance not much better than that of patients in the non-compliance group, and with relatively poor compliance by contrast with those PH-negative patients in the compliance group. There was no wonder that no positive difference was found for PH-related variables between the two subgroups. From another perspective, this result reflected that poor compliance with LTOT was not beneficial for the prophylaxis of the development of PH. The last correlation analysis showed that, by the reference of compliance with LTOT, non-compliance was positively correlated with the development of PH due to hypoxic COPD being analogous to the classical prognostic hallmarks of COPD such as GOLD stages or COPD groups,[15] strengthening the cogency of the aforementioned results in this study.

Due to the poor prevalence of RHC in patients with COPD, we believe that the strength of this study was that all patients being studied had a negative diagnosis of PH at baseline and a positive or negative diagnosis of PH at enrollment, both assessed by RHC. Nevertheless, limitations are unavoidable in this study. First, it was a retrospective study in which some tests and therapies were post hoc instead of being predetermined mandates. In addition, the absence of a control group with placebo in this retrospective review was another defect notwithstanding it would not happen in real-life clinical practice and is liable to be a serious ethical issue in a randomized controlled trial. Moreover, we could not control every aspect of the confounding factors such as the compliance with other COPD-related treatment, irrespective of whether LTOT is believed to be more associated with the development of PH in COPD than other treatments. Second, since RHC is not routinely recommended for patients with COPD,[7] the prevalence of RHC in this population remains inconsiderable. In other words, sample size is not liable to be large as it was in this study. Third, in view of the patients reviewed in this study being all Chinese patients with hypoxic COPD, the results of this study may not be applicable for COPD patients without hypoxemia or for other races. Last, but not least, obviously we have no comments to make on the prophylactic function of LTOT in the prevention of PH due to COPD beyond two years. A large-scale prospective randomized controlled trial may be warranted in the future.

In summary, in this retrospective review, we found that for patients with PH due to COPD with hypoxemia, excellent compliance with adherence to LTOT is more liable to lower the risk and postpone the development of PH due to COPD for at least two years compared with poor compliance. From the perspective of lowering the risk and suspending the development of PH due to COPD, the adherence to continuous LTOT for >15 h per day can be regarded as one of the potentially prophylactic regimens available to date.

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